REMARKS

Claims 1-34, 37 and 40-57 were pending prior to this response, with claims 1-33 and 41-56 being withdrawn due to a restriction requirement. By the present communication, 1-33, 37 and 41-57 have been cancelled, and claims 34 and 40 have been amended to define Applicants' invention with greater particularity. The claim amendments add no new matter, being fully supported by the Specification and original claims. New claim 58 has been added and is fully supported in paragraph [0074] in the application as filed. Accordingly, claims 34 and 40 are currently pending.

Information Disclosure Statement Mailed April 9, 2003

In response to the Examiner's request in the Office Action, Applicants submit herewith a copy of the Information Disclosure Statement (IDS) with certificate of mailing showing a mailing date of April 9, 2003, references submitted therewith and Form PTO-1449. Applicants respectfully request that the Examiner return an initialed copy of the Form PTO-1449 that was attached thereto, with the next Communication in this case.

The Rejection under 35 U.S.C. § 112, First Paragraph – Enablement

Applicants respectfully traverse rejection of claims 34-40 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Claims 35- 36 and 38-39 have been cancelled, rendering the rejection moot as to those claims. Therefore, Applicants will address the rejection as applied to claims 34 and 40.

Applicants disagree with the Examiner's assertion that the specification fails to contain sufficient description to enable those of skill in the art to make and use the invention without undue experimentation. In particular, Applicants submit that those of skill in the art can readily produce a transgenic mouse that overexpresses APP because a transgenic mouse that overexpresses APP is well known in the art. For example, "the TG2576 transgenic mouse"

overexpresses the 695-amino acid isoforms of human APP (a fivefold increase in A(1-40) and a 14-fold increase in A (1-42/43) and has been known in the art since 1996, as shown by the attached copy of Hsiao et al., "Correlative Memory Deficits, Aϑ Elevation, and Amyloid Plaques in Transgenic Mice" (1996) *Science* 274:99-103. In addition, numerous studies have been conducted by those of skill in the art using the TG2576 transgenic mouse and those of skill in the art are well aware of how to obtain and use a transgenic mouse that overexpresses APP. For example, another group of researchers working independently published a description (after the effective filing date of the application) in which BACE1 knockout mice were prepared and crossed with Tg2576 APP-overexpressing transgenic mice to confirm that a BACE1 knockout mouse generates little APP cleavage products (See attached copy of Luo et al., "Mice deficient in BACE1, the Alzheimer's β-secretase, have normal phenotype and abolished β-amyloid generation," *Nature Neuroscience* (2001) 4(3):231-232). Indeed, Applicants used the same Swedish mutation of the human APP polynucleotide disclosed by Hsiao (See Specification ¶ [0176]) in an adenovirus vector to infect mouse neurons for the in vitro studies contained in the Examples. Also attached for the Examiner's reference is a printout of the first page of the search results obtained by use of the keywords "Tg2576 mouse" in a Google® search. These results show that the Tg2576 mouse was well known by those of skill in the art at the filing of the application and has been used by many to study the mechanisms involved in Alzheimer's disease.

In addition, Applicants' disagree with the Examiner's assertion that the claims at issue encompass agents that both increase and decrease BACE1 activity. The claims as previously presented were amended to recite that equality of production of Aβ1-42 in the transgenic mouse and the BACE1-knockout mouse indicates "an agent that decreases BACE1 activity." To emphasize that the test compound shows a decrease in BACE1 activity, Applicants have further amended the preamble of claim 34 to recite: "A method for identifying an agent that *decreases* the activity of BACE1." Thus it is clear that the invention methods, as recited by amended claim 34, do not encompass agents that would increase the activity of BACE1.

The test for enablement under 35 U.S.C. § 112, first paragraph, is whether the description of the invention is sufficient to enable those of skill in the art to make and use the invention without undue experimentation. Based on the descriptions of the TG2576 mouse in the art at the filing of the present application, Applicants submit that those of skill in the art would have been able to obtain a transgenic mouse that overexpresses APP without undue experimentation. Accordingly, Applicants request reconsideration and withdrawal of the rejection for alleged lack of enablement under 35 U.S.C. § 112, first paragraph.

In view of the claim amendments and the above remarks, Applicants respectfully submit that that subject matter of amended claims 34 and 40 are fully enabled under 35 U.S.C. § 112, first paragraph, and reconsideration and withdrawal of the rejection are respectfully requested.

The Rejection Under 35 U.S.C. § 112, Second Paragraph

Applicants respectfully traverse the rejection of claims 34, 37, 40 and 57 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite due to use of the term "substantially equal" in claim 34. However, to advance prosecution and reduce the issues, Applicants have amended claim 34 to delete the term "substantially equal" and adding the term "similar", thus rendering the grounds for the rejection moot. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

In summary, for the reasons set forth herein, Applicants maintain that claims 34 and 40 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims that are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 677-1456.

Enclosed is Check No. 570017 in the amount of $225.00 in payment of the Two Month Extension of Time Fee. The Commissioner is hereby authorized to charge any other fees that may be associated with this communication, or credit any overpayment, to Deposit Account No. 07-1896. A duplicate copy of this Sheet is enclosed.

Respectfully submitted,

Date: December 13, 2004

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Correlative Memory Deficits, Aβ Elevation, and Amyloid Plaques in Transgenic Mice

Karen Hsiao, * Paul Chapman, Steven Nilsen, Chris Eckman, Yasuo Harigaya, Steven Younkin, Fusheng Yang, Greg Cole

Transgenic mice overexpressing the 695-amino acid isoform of human Alzheimer β-amyloid (Aβ) precursor protein containing a $Lys^{670} \rightarrow Asn$, $Met^{671} \rightarrow Leu$ mutation had normal learning and memory in spatial reference and alternation tasks at 3 months of age but showed impairment by 9 to 10 months of age. A fivefold increase in Aβ(1-40) and a 14-fold increase in Aβ(1-42/43) accompanied the appearance of these behavioral deficits. Numerous Aβ plaques that stained with Congo red dye were present in cortical and limbic structures of mice with elevated amounts of Aβ. The correlative appearance of behavioral, biochemical, and pathological abnormalities reminiscent of Alzheimer's disease in these transgenic mice suggests new opportunities for exploring the pathophysiology and neurobiology of this disease.

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Alzheimer's disease (AD), the most common cause of dementia in aged humans, is a disease of unknown etiology. Amyloid plaques are routinely used for diagnosing AD in brain tissue (1), even though other histologic changes such as neurofibrillary tangles, synaptic and neuronal loss, and

dystrophic neurites are also usually present and sometimes correlate better with dementia (2, 3). The amyloid in senile plaques is composed of Aβ, a 39- to 43-amino acid protein derived from the larger amyloid precursor protein (APP). Small numbers of classic senile plaques develop in the brain with age, but large numbers of senile plaques are found almost exclusively in patients with Alzheimer's type dementia. A diagnosis of AD is made only if both cognitive deterioration and senile plaques are present (4). APP isoforms resulting from alternative splicing form a set of polypeptides ranging from 563 to 770 residues in length. The most abundant of these, APP_{695}, is predominantly expressed in neurons (5) and lacks a Kunitz-protease inhibitor (KPI) domain present in the APP_{751} and APP_{770} isoforms. Five mutations in APP, all located in or near the Aβ domain, have been identified in families with early-onset AD (6, 7, 8, 9, 10).

Transgenic mice (Swiss Webster × C57B6/DBA2) expressing three isoforms of mutant APP (Val^{717} → Phe) with an overrepresentation of KPI-containing isoforms showed Alzheimer-type neuropathology, including abundant thioflavin S-positive Aβ deposits, neuritic plaques, synaptic loss, astrocytosis, and microgliosis (11), but deficits in memory and learning have not yet been reported. Transgenic mice (JU) expressing human wild-type APP_{751} showed deficits in spatial reference and alternation tasks by 12 months of age (12). However, only 4% of aged (≫12 months) transgenic mice exhibited Aβ deposits, and these were rare and diffuse and did not stain with Congo red dye (13). Transgenic mice (FVB/N) overexpressing wild-type and variant human or mouse APP_{695} developed a central nervous system disorder that involved most of the corticolimbic regions of the brain (except the somatosensorimotor area) and resembled an accelerated naturally occurring senescent disorder of FVB/N mice (14). Parameters that influence the phenotype of transgenic mice expressing APP include host strain, APP primary structure, and extent of APP expression (14). We investigated the effects of APP overexpression in C57B6/SJL F_2 mice backcrossed to C57B6 breeders because of their greater longevity compared with FVB/N mice expressing identical transgenes.

Human APP_{695} containing the double mutation Lys^{670} → Asn, Met^{671} → Leu (K670N,M671L; APP_{770} numbering), which was found in a large Swedish family with early-onset AD (10), was inserted into a hamster prion protein (PrP) cosmid vector (15) in which the PrP open reading frame (ORF) was replaced with the variant APP ORF [see (14)]. The resulting mice, Tg(HuAPP695.K670N-M671L)2576, produced 5.56 ± 0.33 units (mean ± SEM; 73-day-old mice) to 5.76 ± 0.74 units (430-day-old mice) of transgenic brain APP expression, where a unit of expression is equivalent to the amount of endogenous mouse APP in nontransgenic (control) littermates (Fig. 1). Transgenic APP expression appeared to remain unchanged between 2 and 14 months of age.

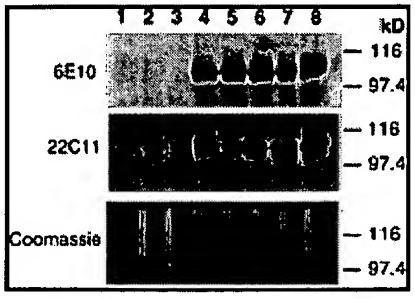

Fig. 1. Brain APP immunoblot of young and old Tg^+ mice and nontransgenic control mice with 6E10 (24), which recognizes human but not mouse APP, and 22C11 (Boehringer Mannheim), which recognizes both human and mouse APP. Lanes 1 to 3, nontransgenic mice; lanes 4 to 6, 73-day-old mice; lanes 7 and 8, 430-day-old mice. Detailed methods for APP quantitation were described previously (14); antibody binding was revealed with ^{35}S-labeled protein A instead of ^{125}I-labeled protein A.

[View Larger Version of this Image (67K GIF file)]

Two groups of 7 to 9 transgene-positive (Tg^+) mice and 10 to 11 transgene-negative (Tg^-) control

littermates underwent spatial alternation testing in a Y-maze at 3 and 10 months of age. Three groups of 9 to 13 Tg^+ mice and 10 to 14 Tg^- littermates underwent spatial reference learning and memory testing in the Morris water maze (16) at 2, 6, and 9 to 10 months of age. The test experience for each set of mice was novel, and all mice were tested in a coded manner. The 9- to 10-month-old mice were N_1-generation mice (C57B6 × C57B6/SJL F_2); the 2- and 6-month-old mice were N_2-generation mice (C57B6 × C57B6 × C57B6/SJL F_2). A subset of the N_2-generation mice (8 transgenic and 10 control mice) were retested at 12 to 15 months of age.

When transgenic and control mice were given a choice of entering either of two arms in a Y-maze, they tended to alternate their choices spontaneously. Ten-month-old transgenic mice, however, showed significantly less tendency ($P < 0.03$) than did age-matched control mice to alternate the arms on successive choices (Fig. 2F). The behavior of the older transgenic mice on the spatial alternation task was characteristic of animals with damage to the hippocampal formation (17).

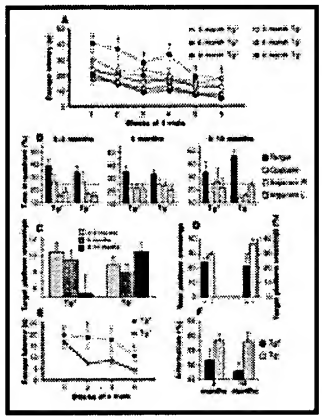

Fig. 2. Learning and memory tests of transgenic and control mice. Asterisks indicate measures in which transgenic mice differed significantly from controls ($P < 0.05$). (**A**) The latency to escape to the hidden platform in the water maze is impaired in Tg^+ mice relative to age-matched nontransgenic controls (19). Although the impairment increases with age, Tg^+ mice showed a consistent trend toward longer escape latencies than those of Tg^- controls. (**B**) After 24 trials (over 6 days) with the platform in its fixed location, mice were given a probe trial in which they swam for 60 s with the platform removed. Two- and 6-month-old Tg^- and Tg^+ mice spent significantly more than 25% of their time in the target quadrant, indicating that they had learned its location. Although 9- to 10-month-old control mice still searched selectively for the platform, older transgenic mice spent no more time in the target quadrant than in the other three quadrants, suggesting that they had not learned the platform's location (20). (**C**) The implications of (B) are supported by the observation that on probe trials, 9- to 10-month-old Tg^+ mice crossed what had been the exact location of the platform significantly less frequently than did age-matched Tg^- mice. (**D**) The bars on the left indicate that transgenic (+) mice did not differ from control (-) mice in the total number of platform locations crossed (that is, the centers of all four quadrants); the bars on the right show the significant difference between 9- to 10-month-old transgenic mice and controls on the percentage of total platform crossings that were over the target. (**E**) Nine- to 10-month-old Tg^+ mice were also impaired in swimming to a visible platform, although escape latencies did not differ significantly on the first visible-platform training trial. (**F**) Aged Tg^+ mice were impaired in their tendency to spontaneously alternate arm-entry in a Y-maze, another behavioral task sensitive to hippocampal damage.
[View Larger Version of this Image (42K GIF file)]

Nine- to 10-month-old transgenic mice were also impaired in their performance in the water maze relative to age-matched controls (18) (Fig. 2). The performance of transgenic mice trained and tested at 2 or 6 months of age was not significantly different from that of age-matched control mice on most measures. The amount of time taken by the mice to reach the hidden platform (the escape latency) did not differ between 2-month-old transgenic and control mice at any point during training, whereas the latency was significantly different on every day for 9- to 10-month-old mice (19). Six-month-old transgenic mice differed from controls in escape latency only on the last day of training. After the last

training day (day 6), all mice were given a probe trial, in which they swam in the pool for 60 s with the platform removed (20). One measure of the animals' knowledge of platform location is the percentage of the 60-s swim spent in the target quadrant (the quadrant that held the platform during training; Fig. 2B). Because the platform is placed in the center of the target quadrant during training, an additional measure that has proven especially useful for mice involves recording the number of times they cross the center of each quadrant. The number of times each mouse crossed the center of the target quadrant (platform crossings; Fig. 2C) and the percentage of total quadrant center crossings that were in the target quadrant were both significantly different [21.5 ± 5.2% for transgenic mice versus 36.1 ± 3.9% for control mice ($P < 0.05$), where 25% is performance at the level of chance] (Fig. 2D) for 9- to 10-month-old transgenic mice compared with age-matched controls.

When 12- to 15-month-old N_2-generation transgenic mice were retested in the water maze (after rearranging the extramaze cues), they showed significantly impaired performance ($P < 0.05$) compared with control littermates on escape latencies after the fifth trial block and on probe trials given after the sixth and ninth trial blocks. These data suggest that the age-related learning impairment seen in N_1-generation Tg^+ mice can occur despite further genetic dilution of the SJL strain. Although the escape latencies of the transgenic N_2-generation mice were significantly longer than those of their control littermates, they were also shorter than those of naïve Tg^+ mice of comparable age. Thus, deficits in escape latency in aged transgenic mice are unlikely to result from difficulty in swimming, as aged mice given sufficient practice can swim as well as younger mice.

Because it is possible that the performance of older transgenic mice was attributable to sensory or motor impairments, we also tested 9- to 10-month-old mice on the visible-platform version of the water maze (Fig. 2E). Although differences in escape latency were evident on the second and fourth of four training days, there were no differences on day 1. These data suggest that although older transgenic mice may show generalized cognitive impairment, they are capable of performing as well as controls when both are relatively naïve. We also compared motor performance of the transgenic and control 9-month-old mice by scoring the total number of times during the probe trial that each mouse crossed imaginary platforms located in each of the four quadrants. If impaired mice swim normally but in a random pattern during probe trials, they should cross the center of all four quadrants combined as many times as would unimpaired mice; they will simply cross the target platform fewer times. If, on the other hand, they are impaired on probe trials simply because they are not swimming, there will be fewer total platform crossings. In fact, the total numbers of platform crossings for transgenic mice (24.4 ± 8.7, mean ± SEM) and control mice (29.5 ± 1.4) were not significantly different, which indicated that motor impairment was not a cause of poor performance in the water maze (Fig. 2D).

After behavioral testing, a subset of each group of mice was killed painlessly. One hemibrain was frozen for cerebral cortical Aβ measurements, and the other hemibrain was immersion-fixed for histopathological analysis. All brains were analyzed in a coded fashion. Measurements of Aβ(1-40) and of Aβ(1-42/43) were done with the use of either the Ban-50/Ba-27 or Ban-50/Bc-05 enzyme-linked immunosorbent assay (ELISA) systems (21, 22). These measurements showed a fivefold increase in the concentration of Aβ(1-40) ($P = 0.03$, rank sum test) and a 14-fold increase in that of Aβ (1-42/43) ($P = 0.03$, rank sum test) between the youngest (2 to 8 months) and oldest (11 to 13 months) Tg^+ mice (Table 1). Thus, there was an association between significantly elevated amounts of Aβ and the appearance of memory and learning deficits in the oldest group of transgenic mice.

Table 1. Concentrations of Aβ in transgenic and control mouse brains. Brain tissue was stained with monoclonal antibody (mAb) 4G8 (25), which recognizes both mouse and human Aβ. All amyloid deposits stained with 6E10 (24), which specifically recognizes human Aβ. No extracellular 6E10 staining was detected in three 105- to 106-day-old Tg^+ mice or one 155-day-old Tg^+ mouse (A01480, A01547, A01548, and Tg2576 founder). ++, 2 to 5 plaques per section; +++, 6 to 10 plaques per section; ++++, >10 plaques per section; -, no staining. Because all the pathological specimens were analyzed in a coded fashion, some nonspecific, equivocal staining that could not be blocked by preabsorption of the antibody with specific peptides was observed in some sections (indicated by ±).

Mouse number	Transgene	Age when killed (days)	Aβ(1-40) (pmol/g)	Aβ(1-42/43) (pmol/g)	Amyloid plaques
		Mice killed at 11 to 13 months of age			
A01484	+	361	325	219	+++
A01488	+	354	192	129	++
A01489	−	354	<2	<2	±
A01492	−	371	<2	<2	−
A01493	+	368	273	177	++++
A01495	−	354	<2	<2	−
A01496	−	354	<2	<2	±
Mean (±SEM) Aβ concentration in Tg^+ mice:			264 ± 38	175 ± 26	
		Mice killed at 6 to 8 months of age			
A01984	−	233	<2	<2	±
A01987	−	219	<2	<2	−
A01989	+	219	45	18	−
A02561	−	214	<2	<2	
A02595	−	207	<2	<2	
		Mice killed at 2 to 5 months of age			
A02428	−	139	<2	<2	−
A02429	−	139	<2	<2	
A02430	−	139	<2	<2	−
A02565	+	118	71	21	
A02900	−	85	<2	<2	
A03103	+	67	32	2	
A03107	+	67	45	10	
Mean (±SEM) Aβ concentration in Tg^+ mice:			48 ± 8	13 ± 4	

Classic senile plaques (with dense amyloid cores) and diffuse deposits were both present in all three mice with elevated Aβ, as determined by ELISA. The Aβ deposits were immunoreactive with antibodies recognizing Aβ(1-5) (23), Aβ(1-17) (24), Aβ(17-24) (25), Aβ(34-40) (26), Aβ(42/43) (27), and free Aβ42 (28). The same plaques were readily identified with multiple antibodies on adjacent

sections and were not seen with preimmune or nonspecific ascites, and the immunoreactivity was eliminated by preabsorption with the relevant peptides (Fig. 3). Deposits could not be found in the older or younger controls or in the younger transgenic mice examined. The deposits were found in frontal, temporal, and entorhinal cortex, hippocampus, presubiculum, subiculum, and cerebellum, in a pattern similar to that reported by Games *et al.* (11). Dense amyloid plaques were most frequent in cortex, subiculum, and presubiculum. The dense amyloid deposits were readily detected with thioflavin S fluorescence and typically could also be labeled with Congo red to give the characteristic apple-green birefringence of classical amyloid (29). Some small deposits had the "Maltese cross" signature pattern of the amyloid cores found in AD brains. Under high magnification, the thioflavin S- and Congo red-positive amyloid plaques usually exhibited wisps or fibers radiating from the central mass, which was often ringed by glial nuclei with both astrocytic and microglial morphology. Glial fibrillary acidic protein-immunoreactive astrocytes were associated with amyloid deposition. Staining by the Gallyas silver method revealed dystrophic neurites surrounding dense core plaques.

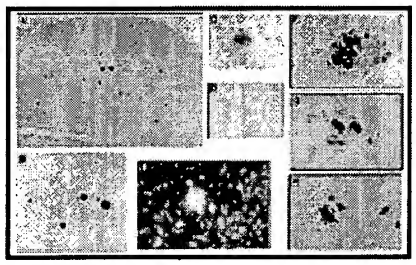

Fig. 3. Extracellular amyloid deposits in transgenic mice A01493 (age, 368 days) and A01488 (354 days) overexpressing human APP_{695} with the K670N,M671L mutation. (**A**) A01493, multiple plaques in the cerebral cortex and subiculum staining with 4G8 mAb. (**B**) A01493, inset from (A). (**C**) A01488, plaque in subiculum staining with 4G8 mAb. (**D**) A01488, plaque in section adjacent to (C) fails to stain with 4G8 mAb preabsorbed with Aβ (14-24). (**E**) A01488, plaques staining with thioflavin S. (**F**) A01488, plaque staining with Aβ(1) affinity-purified antiserum specifically recognizing the NH_2-terminus of Aβ. (**G**) A01488, plaque staining with Aβ(42) affinity-purified antiserum specifically recognizing the COOH-terminus of Aβ(1-42). (**H**) A01488, plaque staining with α40 affinitypurified antiserum specifically recognizing the COOH-terminus of Aβ(1-40). Magnifications: ×100 (A), ×250 (B), ×1000 (C, D, F, and G), ×640 (E), and ×500 (H). [View Larger Version of this Image (93K GIF file)]

In contrast to plaques from patients with sporadic AD, antibodies to β1 and to both free Aβ(42) and Aβ (34-40) (which preferentially recognizes x-40) labeled the majority of deposits. This may reflect the $APP_{670-671}$ mutations, which greatly increase cleavage at the β1 site, leading to large concentrations of all fragments beginning with the β1 epitope. In contrast, the $Val^{717} \rightarrow$ Phe mutations increase the percentage of x-42 (21, 30).

Our results demonstrate the feasibility of creating transgenic mice with robust behavioral and pathological features resembling those found in AD. Impairment in learning and memory became apparent in mice 9 months of age and older; this impairment was correlated with markedly increased amounts of Aβ and was accompanied by numerous amyloid plaques and Aβ deposits. We have demonstrated that an APP transgene lacking the KPI domain is also capable of engendering amyloid plaques in mice. The increase in the concentration of Aβ cannot be explained by a rise in transgenic APP expression, which appeared to remain unchanged with age. Concentrations of Aβ(1-42/43) rose more markedly than did those of Aβ(1-40). This result parallels the finding in humans with presenilin 1 and presenilin 2 mutations showing more significant elevations of Aβ(1-42/43) than of Aβ(1-40) in serum and cultured fibroblasts (31). Studies correlating individual performance in learning and memory tests with concentration of Aβ and extent of amyloid deposition may help to ascertain the contribution of each parameter to behavioral deficits. Whether the learning and memory deficits in these mice are caused by or merely correlate with a rise in brain Aβ levels and amyloid deposition remains unresolved.

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18. The water maze was a circular pool (diameter 1 m) filled with water maintained at 29°C and made opaque by the addition of powdered milk. Mice were pretrained by swimming to a 12.7 cm by 12.7 cm Plexiglas platform that was submerged 1.5 cm beneath the surface of the water and placed at random locations within the pool. During pretraining, heavy curtains were drawn around the pool so that mice were unfamiliar with the extramaze room cues on the first day of spatial training. Spatial training consisted of four trials per day, each trial lasting until the mouse reached the platform or 60 s, whichever came first. After each trial, mice remained on the platform for 30 s. Twenty-four hours after the 12th and 24th trials, all mice were subjected to a probe trial in which they swam for 60 s in the pool with the platform removed. Mice were monitored by a camera mounted in the ceiling directly above the pool, and all trials were stored on videotape for subsequent analysis of platform crossings and percent time spent in each quadrant during probe trials. Visible-platform training—in the same pool but with a platform that was black, slightly larger (14.2 cm by 14.2 cm), and raised above the surface of the water —was given at least 24 hours after the second probe trial. The platform location was varied randomly from trial to trial to eliminate the potentially confounding contribution of extramaze spatial cues. In both visible-platform and hidden-platform versions, mice were placed in the pool facing toward the wall of the pool in one of seven randomly selected locations. The numbers of mice tested in the water maze were 12 transgenic and 12 controls at 2 months, 13 transgenic and 14 controls at 6 months, and 9 transgenic and 10 controls at 9 to 10 months of age.
19. The escape latency data were examined with a multifactor analysis of variance (ANOVA) including genotype (transgenic vs. control), age (2 months, 6 months, or 9 to 10 months), and training day (four trials per day). The ANOVA revealed significant main effects of genotype [$F(1, 384) = 65.19$, $P < 0.0001$], age [$F(2, 384) = 7.64$, $P < 0.001$], and trial block [$F(5, 384) = 12.20$, $P < 0.0001$]. Moreover, there was a significant interaction between genotype and age [$F(2, 384) = 10.13$, $P < 0.0001$], indicating that the transgene-induced impairment of escape

latency increases with age.
20. All mice were also given a probe trial after 12 training trials (3 days at four trials per day). However, neither the transgenic nor the control mice had learned to search selectively after only 12 trials. The early probe trial was necessary because of the possibility of transient differences manifested only early in training, and because of the likelihood that we would have missed these differences because all behavioral tests were conducted blind to genotype. As none of the mice learned the task, there were no differences among any groups; for the sake of clarity, these data have not been presented graphically.
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Mice deficient in BACE1, the Alzheimer's β-secretase, have normal phenotype and abolished β-amyloid generation

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Mice deficient in BACE1 (beta-site APP cleaving enzyme 1) are healthy, fertile and appear normal in gross anatomy, tissue histology, hematology and clinical chemistry. BACE1$^{-/-}$ mice also hemizygous for an amyloid precursor protein (APP) transgene lack brain β-amyloid (Aβ) and β-secretase-cleaved APP C-terminal fragments (CTFs). These results provide validation of BACE1 as the major β-secretase *in vivo* and suggest that therapeutic inhibition of BACE1 for the treatment of Alzheimer's disease may be free of mechanism-based toxicity.

Cerebral amyloid plaques, characteristic lesions found in Alzheimer's disease, are extracellular deposits of Aβ, a 40–42 amino acid peptide generated by endoproteolysis of the Type I membrane protein, APP (for reviews, see refs 1 and 2). Aβ formation involves the sequential cleavage of APP by two proteases, the β- and γ-secretases (for review, see ref. 3). β-secretase cleaves first to form the N-terminus of Aβ, and the resulting membrane-bound fragment, C99, is then cut by γ-secretase to produce the C-terminus of the mature peptide. Although the role of Aβ in Alzheimer's disease has been intensely debated, evidence suggests that Aβ is central to Alzheimer's disease pathogenesis. Consequently, the β- and γ-secretases are prime drug targets for the treatment of Alzheimer's disease.

The novel aspartic protease BACE1 is as an excellent β-secretase candidate[4–7]. Shortly after the discovery of BACE1, the homolog BACE2 was identified[8,9], which is highly similar to BACE1. Although the expression pattern of BACE2 does not fit that of β-secretase[9], BACE2 cleaves APP substrates at the β-secretase site *in vitro*[10], suggesting a potential involvement in Aβ generation.

To validate BACE1 as the major β-secretase *in vivo*, and to determine if BACE1 deficiency causes mechanism-based toxicity, we generated BACE1-deficient mice by gene targeting. (For methods and characterization, see supplementary information on the *Nature Neuroscience* web site.) Inter-crosses of BACE1$^{+/-}$ mice produced BACE1$^{-/-}$ mice in the normal Mendelian frequency of ~25%. BACE1$^{-/-}$ mice are healthy, fertile and appear normal. Northern blot analysis revealed that the three major mouse BACE1 transcripts (~4.0, 4.4 and 7.0 kb) were barely detectable in BACE1$^{-/-}$ brain mRNA samples, and BACE1 protein was undetectable in BACE1$^{-/-}$ brain extracts by immunoprecipitation (IP)-western blot analysis.

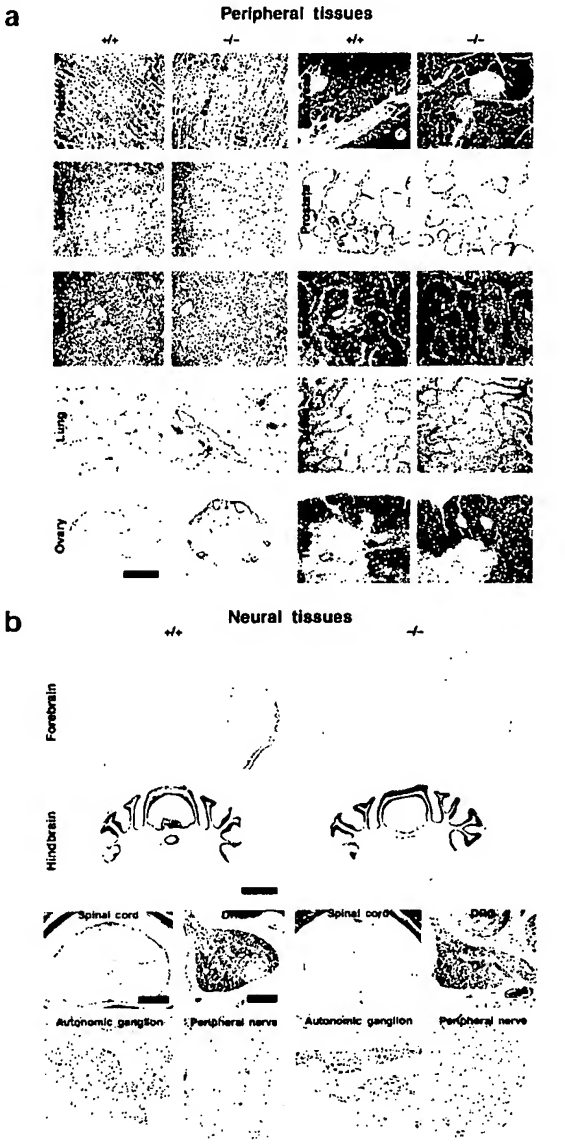

Fig. 1. BACE1 deficiency does not affect morphology of neural or non-neural tissues. Tissue sections from ~3–4 month old BACE1$^{+/+}$ and BACE1$^{-/-}$ mice stained with either hematoxylin and eosin, or cresyl violet (brain). (a) Non-neural tissues. Specific tissue is indicated at left of each pair of panels. Scale bar, 100 μm for all sections. (b) Neural tissues. Top four panels, coronal sections of forebrain and hindbrain from BACE1$^{+/+}$ and BACE1$^{-/-}$ mice. Bottom panels, sections through spinal cord, dorsal root ganglion (DRG), autonomic ganglion and peripheral (sciatic) nerve of BACE1$^{+/+}$ and BACE1$^{-/-}$ mice. Scale bars, 100, 50 and 25 μm for brains, spinal cords and ganglia/nerve, respectively.

(See Supplementary Fig. 2 on the *Nature Neuroscience* web site).

To determine whether BACE1$^{-/-}$ mice exhibit subtle anatomical or physiological abnormalities, we performed extensive pathology analyses of BACE1$^{-/-}$ mice. Five (BACE$^{+/-}$; 2 males and 3 females) to seven (BACE$^{+/+}$ and BACE$^{-/-}$; 4 males and 3 females) mice approximately 3–4 months old were examined for each genotype. No abnormalities were observed upon microscopic examination

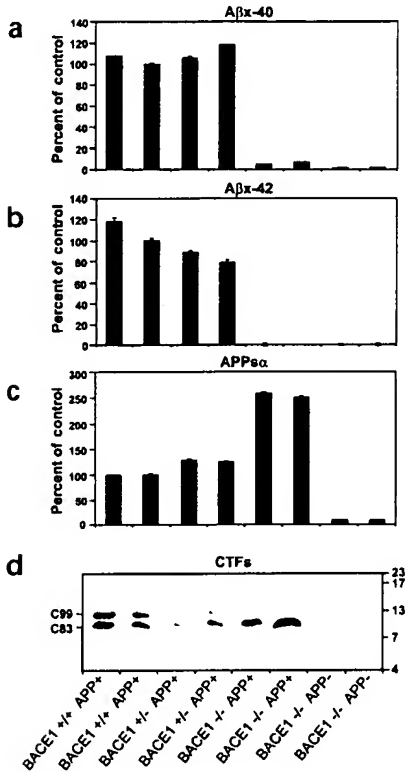

Fig. 2. BACE1 deficiency abrogates brain Aβ. Brains from BACE1$^{+/+}$ APP+ (columns 1 and 2), BACE1$^{+/-}$ APP+ (columns 3 and 4), BACE1$^{-/-}$ APP+ (columns 5 and 6) and BACE1$^{-/-}$ APP- (columns 7 and 8) mice (2 of each genotype) were collected, homogenized and analyzed for Aβx-40 (**a**), Aβx-42 (**b**), and APPsα (**c**) by ELISA, and APP CTFs by western blotting with an APP C-terminal antiserum (**d**). Values for (**a–c**) are percent of control, where 100% is BACE1$^{+/+}$ APP+. Error bars, standard deviation of 2 (Aβx-40 and Aβx-42) or 4 (APPsα) measurements per sample. In (**d**), β- and α-secretase-cleaved APP CTFs, C99 and C83 respectively, are indicated at left, and molecular weight markers are indicated in kilodaltons at right. Genotypes of mice are indicated at the bottom of (**d**) and are the same in all frames.

of sections from neural (central and peripheral) or non-neural tissues of BACE1$^{-/-}$ mice (Fig. 1a and b). In addition, clinical chemistry analytes were comparable for animals of all genotypes, and hematology analysis revealed no alterations in blood cell lineages in BACE1$^{-/-}$ mice. (For supplementary information, see the *Nature Neuroscience* web site.) To date, our oldest BACE1$^{-/-}$ mice are over one year old, and they do not exhibit any obvious physical or behavioral differences as compared to age-matched control mice. Thus, under normal conditions, BACE1 deficiency does not seem to be associated with any discernable abnormality in mouse, at least for the parameters examined.

If BACE1 is the major β-secretase *in vivo*, then BACE1$^{-/-}$ mice should generate little Aβ, if any. To facilitate the detection of Aβ *in vivo*, we crossed Tg2576 APP-overexpressing transgenic mice[11], which develop amyloid plaques by 9–10 months of age, with BACE1$^{-/-}$ mice. The brains of 2–3-month-old BACE1$^{-/-}$, BACE1$^{+/-}$ and BACE1$^{+/+}$ offspring that were also hemizygous for the Tg2576 transgene (APP+) were collected, and brain extracts were prepared. At this age, Tg2576 mice show high levels of soluble Aβ in brain, but plaque formation has not yet begun[11]. Extracts were measured by ELISA for Aβx-40, Aβx-42 and the secreted ectodomain of APP generated by α-secretase, APPsα[4] (Fig. 2a–c). In addition, western blot analysis of brain homogenates was done to examine the APP CTFs (Fig. 2d) produced by β-secretase (C99 and C89) and α-secretase (C83).

Aβx-40 levels in BACE1$^{-/-}$ APP+ extracts were only ~5–7% of those in BACE1$^{+/+}$ APP+ or BACE1$^{+/-}$ APP+ homogenates (Fig. 2a). Moreover, Aβx-42 was undetectable in BACE1$^{-/-}$ APP+ extracts (Fig. 2b). APPsα levels were increased over twofold in BACE1$^{-/-}$ APP+ extracts, as compared to BACE1$^{+/+}$ homogenates (Fig. 2c). This result is similar to the elevation of APPsα observed upon antisense inhibition of BACE1 in cells[4], and suggests that α- and β-secretases compete for APP substrate *in vivo*.

Western blot analysis of APP CTFs demonstrated that C99 was absent in BACE1$^{-/-}$ APP+ brains (Fig. 2d). In contrast, C83 was present in all APP+ samples and even seemed elevated in BACE1$^{-/-}$ APP+ homogenates. C89, the CTF produced by β-secretase cleavage at Glu11 of Aβ[12,13], was not observed in any of the samples, indicating that Asp1 cleavage is predominant in APP+ brains. Both of the β-secretase-cleaved CTFs, C99 and C89, were absent in BACE1$^{-/-}$ APP+ brains.

Here we show that BACE1-deficient mice lack Aβ- and β-secretase-cleaved APP CTFs in the brain. These results provide validation of BACE1 as the major β-secretase *in vivo*, and indicate that BACE2 (or any other enzyme) is not significant in β-secretase cleavage. Moreover, BACE1$^{-/-}$ mice are normal in appearance and behavior, and are healthy and fertile. Although our phenotypic analyses revealed no discernable abnormalities in BACE1$^{-/-}$ mice, we cannot exclude the possibility that specific phenotypes may develop after challenging BACE1$^{-/-}$ mice under certain conditions of stress. However, at this point, we conclude that, under normal conditions, BACE1 does not have a vital function *in vivo* for which no redundancy exists.

We found the viability of BACE1$^{-/-}$ mice to be very surprising, because BACE1 is expressed at low levels in most tissues, and is highly expressed in brain and pancreas[4,5]. Whereas such principal considerations could be raised about any widely expressed target, the possibility of mechanism-based toxicity has become an intensely debated issue for the γ-secretase, which controls vital Notch signaling (for review, see refs. 14 and 15). However, the finding that there are no apparent adverse effects associated with BACE1 deficiency in mice suggests that inhibition of BACE1 in humans may not have mechanism-based toxicity. Of course, the final resolution of this issue will require the testing of BACE1 inhibitors in human clinical trials.

Note: Supplementary information is available on the Nature Neuroscience web site (http://neurosci.nature.com/web_specials/).

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